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Title: Heart Rate Variability Analysis in the Assessment of Autonomic Function in Heart Failure

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Abstract

Heart rate is not static but rather changes continuously in response to physical and mental demands. In fact, an invariant heart rate is associated with disease processes such as heart failure. Heart rate variability analysis is a noninvasive technique used to quantify fluctuations in heart rate. In this paper, we review neural control of heart rate, briefly describe heart rate variability, and summarize research data demonstrating that heart failure is associated with altered heart rate variability. In addition, we present evidence that heart failure patients with decreased heart rate variability are at risk for future cardiac events, need for heart transplantation, and death.

Key Words: Heart failure, heart rate variability, autonomic nervous system

Clinicians often report that a patient's heart rate (HR) is "regular." Yet, as shown in Figure 1, HR is not a static hemodynamic parameter, but rather changes over time in response to physical and mental demands. Furthermore, an invariant, or nearly invariant, HR is often associated with disease processes such as heart failure (HF),[1-5] acute myocardial infarction (AMI),[6-10] and diabetes.[11] Heart rate variability (HRV) analysis is a noninvasive technique used to quantify fluctuations in HR that reflect naturally occurring physiological processes.[12] The purpose of this paper is to review neural control of HR, briefly describe HRV, and summarize research findings about HRV for patients with HF.

Neural Control of Heart Rate

Heart rate is normally determined by spontaneous and periodic depolarizations of the sino-atrial node. Although neural innervation is not necessary to initiate the heart beat, the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS), the intrinsic cardiac nervous system, reflexes, and respiration modulate the frequency of sino-atrial nodal depolarizations. These neural systems also influence cardiac contractility and conduction of electrical activity through the heart. Accordingly, cardiac chronotropism (HR), inotropism (contractility), and dromotropism (conduction, primarily through the AV node) are adjusted to meet the changing needs of the body.

Sympathetic Nervous System

Sympathetic nervous system fibers emerge from the cell bodies of preganglionic neurons within the intermediolateral column of the spinal cord located in the thoracic through lumbar (T1-L2) regions. After passing through the white rami, most fibers synapse with postganglionic efferent neurons within the sympathetic paravertebral ganglia. The axons of these postganglionic neurons innervate blood vessels and the viscera.[13]

Parasympathetic Nervous System

Parasympathetic nervous system fibers emerge from cell bodies of the preganglionic neurons located in the brainstem and sacral area (S2-S4). Parasympathetic nerves travel to the head, thorax, and abdomen within cranial nerves. The vagus nerve (i.e, cranial nerve X) provides the parasympathetic innervation to the heart, lungs, and some abdominal regions. The majority of the axons within this nerve are sensory (i.e., visceral afferent); only about 20% of these axons are motor (i.e., parasympathetic efferent).

Like sympathetic nerves, the vagus nerve innervates the sinus and atrioventricular nodes and the atrial myocardium. The classical view that there is little to no parasympathetic innervation of ventricular myocardium neglects the well-established fact that parasympathetic nerves presynaptically inhibit the release of neurotransmitter from sympathetic nerves innervating ventricular myocardium; this "indirect" effect can profoundly affect ventricular contractile function.[13-15] Vagal stimulation promotes acetylcholine release which decreases HR, myocardial conduction, atrial contractility, and through interaction with the sympathetic system, ventricular contractility.[13,14]

Functional Connectivity Between the Sympathetic and Parasympathetic Systems

The heart and the majority of other organs are innervated by both sympathetic and parasympathetic nerves (i.e., reciprocal innervation). In resting man, parasympathetic effects predominate sympathetic effects on HR. Whereas activity in the cardiac parasympathetic efferent nerves produces changes in HR on a beat to beat basis,[16] typically, many seconds elapse before changes in cardiac sympathetic nervous activity achieve peak effects. Thus, as is explained below, these short latency effects of vagal activation ultimately explain the dominance of the parasympathetic nervous system within the "high frequency" range of the HR power

spectrum. Conversely, alterations in sympathetic activity produce large amplitude, but slowly developing, or "low frequency" changes in HR. In general, sympathetic stimulation is associated with diminished parasympathetic activity; the opposite is also true.[17]

Intrinsic Cardiac Nervous System

Recently, the anatomy of function of a nervous network within the heart itself has been extensively studied. Intrinsic cardiac ganglia have been described in five regions on the posterior surface of the atria and in five regions on the superior aspect of the ventricles.[18] The ICN reportedly includes not only the classically described parasympathetic post-ganglionic neurons, but also sensory neurons, interneurons and catecholaminergic (i.e., "sympathetic") neurons. The "intrinsic cardiac network" (ICN) formed by these elements is effectually a localized component of the ANS analogous to the enteric nervous system in the gut. The cardiac ICN appears to be capable of mediating intracardiac reflexes.[14] Canines with early-stage HF manifested altered intrinsic cardiac nervous function and a compromised ability to regulate HR and other hemodynamic variables.[19] Thus, neural control of HR is likely a function of both the intrinsic cardiac and autonomic nervous systems.[15]

Autonomic Neuropharmacology

Norepinephrine is released from the sympathetic nerve varicosities; it interacts with β adrenergic receptors in the heart to produce positive chronotropic, dromotropic or inotropic effects, depending upon the tissue under consideration. Newer evidence has shown that the heart itself synthesizes norepinephrine.[20,21] Parasympathetic post-ganglionic fibers release acetylcholine that then interacts with muscarinic cholinergic receptors. Activation of these receptors, again depending upon the specific tissue, produces negative chronotropic, dromotropic and, in the atria, inotropic effects. Although their function has not been fully elucidated, it is

known that numerous putative neurotransmitters are co-released with these "classical" neurotransmitters. These include, for example, adenosine 5'-triphosphate, adenosine, 5-hydroxytryptamine, neuropeptide Y, vasoactive intestinal polypeptide, somatostatin, nitric oxide, carbon monoxide, and histamine.[22]

Reflex Control of Cardiovascular Function

Receptors within the aortic arch and carotid sinus sense blood pressure changes and modify HR to maintain hemodynamic stability. For example, if blood pressure increases, the baroreceptors fire more rapidly and transmit impulses to the nucleus tractus solitarius (NTS) in the brainstem.[23] Neurons from the NTS project to the nucleus ambiguus and stimulate parasympathetic preganglionic neurons which, in turn, project through the vagus nerve to parasympathetic ganglia at the heart.[23] At the same time, activity within the sympathetic nerves is decreased. As a result, HR, peripheral vascular resistance, and cardiac output decrease and blood pressure normalizes.

Increased right atrial pressure distends atrial mechanoreceptors which transmit impulses to the brainstem via vagal afferent nerves. Unlike the baroreflex, this Bainbridge reflex is a "feed forward" mechanism whereby efferent sympathetic stimulation produces tachycardia and thus enables the heart to effectively pump the larger preload. However, the magnitude and direction of the HR response depend on the baseline HR and concomitant baroreceptor reflex activity.[13]

Respiratory Sinus Arrhythmia

Respiratory sinus arrhythmia (RSA) refers to the cyclical variation in HR interval associated with respiration and is primarily attributable to oscillations in efferent activity in the vagal fibers innervating the sino-atrial node (Figure 2).[24] During inspiration, lung distention

stimulates vagal afferent nerves in the lungs. In the brainstem, these vagal sensory impulses ultimately inhibit vagal efferent activity, thereby increasing HR. With expiration, HR decreases secondary to increased cardiac vagal activity. This is one mechanism whereby breathing has a profound impact on HR fluctuations.[25] Other data suggest that sympathetic activity also influences RSA at both slow and rapid breathing rates.[26] Respiratory sinus arrhythmia may improve the efficiency of pulmonary gas exchange.[27]

Heart Rate Variability

The RR interval on the electrocardiogram (ECG) is the time between two ventricular beats and thus can be used to calculate ventricular rate. For example, the RR interval is 0.8 sec when HR is 75 beats/min. Heart rate variability refers to the increases and decreases over time in the RR interval.[28,29] Very slowly occurring changes in the RR interval have been attributed to alterations in vasomotor tone associated with thermoregulation.[30,31] More rapid changes in the RR interval are produced by the baroreceptor reflex.[24] As has already been explained, rather rapid changes in RR interval are produced by respiration. Normal aging is associated with decreased HRV.[32] Much of the current interest in HRV stems from reports that "power" within select frequency ranges provides evidence regarding the ANS and its effectors. Although HRV analysis does not directly measure autonomic nervous activity,[33] HRV data have prognostic value for patients with HF.[1,4,34-36]

The first step of HRV analysis is to acquire a quality ECG recording; for typical applications, an artifact-free recording of five minutes' duration is generally adequate, although longer data sets are required in more specialized circumstances.[37] Using a computer and commercial software, the ECG analog signal is then converted to a digital signal. The computer also generates the RR tachogram which is a series of time intervals between two consecutive R

waves. Time-domain and frequency-domain analyses are the approaches most often used to quantify HRV. Nonlinear methods such as Poincaré plots have also been used to study patients with HF,[38,39] though this methodology will not be considered here.

Time-Domain Analyses

Time-domain analyses are statistical calculations of RR intervals (also termed normal-to-normal [NN] intervals) and are relatively easy to compute. Using the RR tachogram, computer software calculates the sequential NN intervals of adjacent R waves produced by a sinus pacemaker; any ventricular ectopic beats are edited from the record. The software also computes the differences between NN intervals. Other time-domain measures that can then be derived include: 1) standard deviation of all NN intervals for a selected time period (SDNN), 2) standard deviation of the mean of NN intervals in all 5-minute segments of the recording period (SDANN), 3) square root of the mean squared differences of successive NN intervals (RMSSD), 4) the number of pairs of successive NN intervals differing by greater than 50 ms in the recording period (NN50 count), and 5) the proportion of differences in successive NN intervals greater than 50 ms (pNN50).[28] Although most investigators calculate pNN50 values, in one study NN12 values best differentiated between healthy persons and patients with HF.[2] In the same study, patients with New York Heart Association (NYHA) class I-II HF had higher pNN10, but not pNN50, values than patients with class III-IV HF. Numerically smaller time-domain values denote lower HRV.

Frequency-Domain Analysis

For frequency-domain (or spectral) analysis of the RR tachogram, computer software uses an mathematical algorithm, such as fast Fourier transformation, to apportion the HRV signal into its frequency components (Figure 3) and to quantify the power of these components. To

understand this process more clearly, consider that any "signal" contains information that ranges from components that change very slowly (i.e., low frequency) to components that fluctuate rapidly. The relative admixture of the various frequency components is often of considerable importance. For example, the overall sound generated by a mixed choir of male and female voices includes the very low frequencies of the base section, the somewhat higher frequencies of the tenors, as well as the much higher frequencies produced by the alto and soprano singers. The conductor, in analyzing the quality of the performance, can mentally perform a "frequency domain analysis" to discern the individual notes produced by each section (e.g., are the tenors "in tune?"), and assess the intensity of each part (e.g., is the mixture of the volume of sound from the bases and sopranos appropriately balanced?). Likewise, spectral, or frequency-domain analysis, precisely quantifies the power of fluctuations in HR over a designated range of frequencies.[40] Unlike time-domain measures, frequency-domain measures can quantitate rhythms and their frequencies.[25]

Frequency-domain results are displayed by plotting the magnitude of HRV power against frequency. Three frequency bands are of clinical interest: 1) very-low frequency (VLF) band (0.003-0.04 Hz), 2) low frequency (LF) band (0.04-0.15 Hz), and 3) high frequency band (0.15-0.4 Hz).[28] In humans, VLF, LF and high frequency peak frequencies are commonly centered around about 0.015 Hz, 0.1 Hz and 0.25 Hz, respectively. In some contexts an ultra-low frequency band (ULF; ≤ 0.003 Hz) is also of interest.[41,42] Figure 3 is an illustrative heart rate power spectrum computed by a mathematical process known as "Fast Fourier Transform[1]"; it

[1] The computations involved in the Fast Fourier Transform, or FFT, have been included in most of the commercial software that is now widely available for HRV analysis. It is important to bear in mind, however, that there are a number of important requirements for valid computations. For example, any signal subject to FFT must be "stationary," meaning that the statistical characteristics of the signal (e.g., mean value, variance) are the same throughout the course of the recording. The algorithm assumes these conditions have been met, when, in fact, one or more may be violated by a given data set. One must assure him/herself that these requirements are satisfied before performing the computation if valid results are to be obtained.

shows concentrations of power within the three major bands. The area under the curve of each frequency band represents the power within that band. Normally, LF power exceeds high frequency power. Total power represents the variability of the entire signal and is obtained by summing the powers of each frequency band. Low frequency and high frequency power are often "normalized" (i.e., expressed as a percentage of total power), by dividing each by the total power minus VLF power,[43] although in Figure 3 power is given in absolute units of beats-per-minute squared.

Although some have cautioned that respiration itself may be responsible for observed changes in HRV,[24,44,45] it is generally believed that specific physiological processes contribute differently to power within the various regions. For example, it is commonly accepted that respiratory mechanisms mediate high frequency components of HRV.[12,27,46-48] Recall that HR responds very quickly to changes in the nervous activity in the parasympathetic nerves innervating the sino-atrial node. This rapid response characteristic ultimately assures that the HF peak of the HR power spectrum is mediated largely, probably exclusively, by the parasympathetic nervous system.[46] Conversely, the sympathetic system is unable to mediate high frequency components because the sino-atrial nodal response to changes in norepinephrine interacting with the β-adrenergic receptor is much slower than that of acetylcholine interacting with the muscarinic receptors.[40,49] Thus, the high frequency component provides data about how the sino-atrial node responds to vagal activity at the respiratory frequency.

In contrast, a mixture of sympathetic and parasympathetic activities is generally thought to influence the LF components of HRV.[12,46,47] As such, the LF component provides information about autonomic tone; however, evidence suggests that parasympathetic activity dominates at

higher frequencies.[50] The circadian rhythm accounts for much of the variation in the ultra-low frequency band.[51]

Some[17,28,49] investigators argue that the ratio of power within the low frequency vs. high frequency spectral regions (i.e., low frequency:high frequency ratio) distinguishes sympathetic effects from parasympathetic effects. However, this is controversial[48,52] and caution is warranted in drawing any conclusions in this regard. Although the sympathetic and parasympathetic systems function on a reciprocal basis, these systems are not necessarily "balanced."[48]

Heart Rate Variability and Heart Failure

It is well known that a hallmark of HF is adverse changes in autonomic function that are manifested, in part, by altered HRV. Heart failure ensues following myocardial cell damage that impairs ventricular contractility. Neurohormonal systems are activated in an attempt to maintain cardiac output and tissue perfusion.[53] Nonetheless, chronic neurohormonal activation ultimately contributes to progressively deteriorating HF.[53] Fundamentally, HF is characterized by profoundly elevated sympathetic activity for an extended period. Although perhaps less well documented, parasympathetic withdrawal is also an important facet of HF.[47,54]

Heart rate variability analysis enables clinicians and researchers to detect, quantify, and trend changes in autonomic activity for patients with HF. However, spectral analysis is difficult for patients with terminal HF because HR is often nearly invariant.[47]

As shown in Table 1, patients with HF exhibit altered HRV in both the time and frequency domains. High sympathetic activity,[55-57] neuroendocrine dysfunction,[40] elevated cytokine levels,[58] and reduced vagal-cardiac activity[52] contribute to decreased HRV for patients with HF. Patients with decreased HRV have difficulty employing vagal mechanisms to counteract sympathetic activation.[59] Others[60,61] have reported that patients with HF have

decreased LF power which seemingly contradicts the thought that HF is associated with high sympathetic tone. It is possible, therefore, that HRV analysis may be difficult to interpret for groups of individuals, for example, patients with HF compared with healthy persons.

Importantly, decreased HRV is associated with adverse outcomes as shown in Table 2. In summary, time-domain HRV parameters predict mortality[1,4,36,62-65] and future cardiac events.[34] In addition, frequency-domain parameters reportedly predict mortality,[1,35,64,66] sudden death,[5,62] and need for heart transplantation.[67]

Although HRV data are useful, they cannot be interpreted reliably without attention to comorbid conditions,[49] medication therapy,[21] body position,[68] emotions,[69,70] circadian rhythm,[32] and other variables known to affect the ANS. For example, patients with HF had higher high frequency power, lower LF power, and lower HF:LF ratio values in the right lateral decubitus position than in supine or left lateral positions.[68] Moreover, beta-blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists may exert their morbidity and mortality benefits by minimizing ANS and neurohormonal disturbances.[21]

In summary, the sympathetic and parasympathetic nervous systems, reflexes, and respiration influence HR. Heart rate variability analysis enables clinicians and researchers to examine the influences of autonomic activity on HR. A consistent finding for patients with HF is decreased HRV. Importantly, this decreased HRV is associated with adverse outcomes.

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TABLE 1 Research that Indicates Heart Failure is Associated With Decreased Heart Rate Variability

Author/ Date	Major Purpose of the Study Regarding HRV	Sample	Major Findings Related to Heart Rate Variability for Patients with Heart Failure
Saul et al., 1988[71]	Compare the pattern of HRV for patients with severe HF and healthy persons; determine if HRV correlates with hemodynamic and clinical status	25 patients with class III-IV HF; 21 healthy individuals	Patients with HF had a higher mean HR, lower standard deviation of HR, lower SDNN, and lower spectral power in all frequency bands than healthy individuals; in the 0.04-0.07 Hz band, there was a positive relationship between both absolute and fractional power and cardiac index and an inverse relationship between both absolute and fractional power and PCWP
Binkley et al., 1991[54]	Describe the autonomic profile of patients with ventricular dysfunction; evaluate whether patients with ventricular failure have reduced parasympathetic tone	15 healthy men; 10 patients with congestive cardio-myopathy	Healthy men exhibited both HFP and LFP; patients with HF manifested very little HFP, but amplified LFP; after receiving atropine, healthy persons exhibited a significant decrease in HFP; patients with HF had a lower HF:LF ratio than healthy men; fundamentally, parasympathetic withdrawal is a feature of HF
Nolan et al., 1992[72]	Investigate cardiac parasympathetic activity and its association with LV function for patients with HF	43 patients with class II-III HF	To evaluate parasympathetic activity, HRV was measured by counting the number of times that each RR interval was > 50 ms longer than the preceding RR interval; 60% of patients had lower than expected counts; 24 hour RR counts and LVEF were moderately correlated
Szabo et al., 1995[73]	Assess the relationship between severity of HF and changes in HRV	79 patients with HF	NYHA class was inversely correlated with SDNN, SDANN, and LFP; peak VO_2 (ml/min/kg) was positively correlated with SDNN, SDANN, LFP, and HFP; patients with class III-IV HF had lower SDNN, SDANN, and LFP values than patients with class I-II HF; patients with peak $VO_2 < 15.9$ ml/min/kg had lower SDNN, SDANN, HFP, and LFP values than patients with peak $VO_2 > 15.9$ ml/min/kg
Guzzetti et al., 1995[74]	Analyze neural activity of the cardiovascular system in patients with HF	30 patients with class II-IV HF; 15 healthy individuals	Patients with class III or IV HF had lower mean RR values than healthy patients and patients with class II HF; patients with class IV HF had higher HFP (nu) values than other patients and healthy persons; LFP (nu) decreased as HF class increased and was nearly absent in patients with class IV HF; when tilted, healthy persons, but not patients with HF, had decreased RR and HFP (nu) and

Author/ Date	Major Purpose of the Study Regarding HRV	Sample	Major Findings Related to Heart Rate Variability for Patients with Heart Failure
			increased LFP (nu) values; only healthy persons had decreased LFP (nu) with controlled respiration
Fei et al., 1996[75]	Evaluate whether the autonomic nervous system contributes to CI in patients with HF	41 patients with IDC	24% of patients exhibited CI ("an inadequate sinus node response to exercise"); although mean HR was similar, patients with CI had lower SDNN, ln TP, and ln LFP values than patients without CI
van de Borne et al., 1997[60]	Examine sympathetic nerve activity for patients with HF	21 patients with HF; 12 healthy individuals	At LFP, patients with HF had lower RR interval variability and MSNA activity than healthy persons; at HFP, patients with HF had higher RR interval variability and MSNA activity than healthy individuals; Only four patients exhibited LFP
Scalvini et al., 1998[61]	Use HRV to assess autonomic modulation in patients with HF	30 patients with symptomatic class II-IV HF; 21 patients with asymptomatic LVD; 25 healthy individuals	At rest and during sympathetic and parasympathetic stimulation, patients with HF had lower SDRR and absolute and LFP (nu) values than healthy individuals and patients with LVD; at rest, patients with HF had higher HFP (nu) values than persons in the two other groups; patients with HF and asymptomatic LVD did not manifest HRV changes in response to sympathetic stimulation
Atherton et al., 1998[76]	Evaluate whether changes in LVEDV during application of lower-body negative pressure correlate with HRV measures for patients with HF	30 patients with class I-IV HF	During application of lower-body negative pressure, there was a significant negative correlation between change in LVEDV and SDNN, rmsSD, TP, LFP, and HFP
Yoshikawa et al., 1999[56]	Evaluate the relationship among clinical variables, HRV, and baroreceptor sensitivity	146 patients with class I-IV HF	Patients were divided into either a high or low norepinephrine group; patients in the high norepinephrine group had lower ln TP, ln LFP, and ln HFP than patients in the low norepinephrine group; TP and LFP were inversely correlated with norepinephrine level; TP was correlated with plasma renin activity; LFP was correlated with baroreceptor sensitivity
Aronson & Burger, 2000[77]	Explore gender-related differences in HRV for patients with HF	131 men and 68 women with class III-IV HF	Women had higher SDNN, SDANN, RR, ln ULFP, and ln HFP values than men; for patients with nonischemic HF, women had higher SDNN, SDANN, rmsSD, ln TP, ln ULFP, ln VLFP, ln LFP,

Author/ Date	Major Purpose of the Study Regarding HRV	Sample	Major Findings Related to Heart Rate Variability for Patients with Heart Failure
			and ln HFP values than men
Soejima et al., 2000[78]	Determine whether age-corrected HRV can be used as an index of HF severity and prognosis	90 patients with class I-IV HF	Patients were divided into either a control or a patient group based on their LFP and HFP values; patients with LVD had lower ln HFP and ln LFP values than controls; control patients had a higher circadian changes of ln HFP and LF:HF values; ln LFP decreased as HF class increased; in the patient group, HFP did not decrease significantly beyond NYHA class II
Malfatto et al., 2001[79]	Evaluate whether the etiology of HF influences the sympathovagal balance and autonomic responsiveness of patients with HF	21 patients with ischemic HF; 21 patients with IDC	Patients with ischemic HF had higher LFP (nu) and LF:HF ratio values and lower HFP (nu) values than patients with IDC HF at rest and in response to parasympathetic and sympathetic stimuli; patients with ischemic HF had lower LFP and LF:HF ratio and values during parasympathetic stimulation than at rest
Malave et al., 2003[3]	Investigate the relationship between HRV and circulating levels of TNF and norepinephrine	29 patients with class I-IIIa HF; 10 healthy individuals	Patients with class IIIa HF had lower SDNN, SDAN, ln LFP, and HFP values than healthy persons and lower SDNN values than patients with class I-II HF; TNF levels were inversely correlated with SDNN, SDANN, ln LFP, and ln HFP; norepinephrine levels were inversely correlated with SDNN, SDANN, and ln LFP; TNF and ln norepinephrine levels predicted SDNN and LFP values
Musialik-Lydka et al., 2003[80]	Analyze HRV in patients with depressed LVEF; relate HRV to clinical parameters	105 patients with class II-IV HF; 30 healthy individuals	Patients with HF had lower SDNN, SDANN, and rmsSD values than healthy persons; patients with class III-IV HF had lower SDNN and SDANN values than patients with class II HF; NYNA class was negatively correlated with SDNN, SDANN, and rmsSD values; SDNN and SDANN were moderately correlated with LVEF but were stronger for patients with ischemic cardiomyopathy than patients with dilated cardiomyopathy

CI = chronotropic incompetence; HF = heart failure; HFP = high frequency power; HR = heart rate; HRV = heart rate variability; IDC = idiopathic dilated cardiomyopathy; LFP = low frequency power; ln = logarithmic units; nu = normalized units; LV = left ventricular; LVD = left ventricular dysfunction; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; mean RR = mean duration of all normal to normal (NN) RR intervals; MSNA = muscle sympathetic nerve activity; NYHA = New York Heart Association; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; peak VO_2 = peak oxygen consumption;

pNN50 = percentage of adjacent normal RR intervals > 50 ms different; PVC = premature ventricular contraction; rmsSD = square root of the mean of the sum of the squares of differences between adjacent RR intervals; SDNN = standard deviation of all normal RR intervals; SDANN = standard deviation of the averages of RR intervals in all 5-minute segments; SNS = sympathetic nervous system; TNF = tumor necrosis factor; TP = total power; ULFP = ultra-low frequency power; VLFP = very low frequency power

TABLE 2 Research That Indicates Decreased Heart Rate Variability is Associated With Poor Outcomes

Author/ Date	Major Purpose of the Study Regarding HRV	Sample	Major Findings Related to Heart Rate Variability for Patients with Heart Failure
Brouwer et al., 1996[81]	Determine the prognostic value of HRV for patients with mild to moderate HF	95 patients with chronic class II-III HF	No relationship between time and frequency HRV measures and *mortality*; in a multivariate model, abnormal HRV Poincaré plots independently predicted *all-cause cardiac death* and *SCD*
Ponikowski et al., 1997[35]	Evaluate the prognostic value of HRV for patients with moderate to severe HF	102 patients with class II-IV HF	In a multivariate model, SDNN, SDANN, and LFP predicted *cardiac mortality* independently of peak VO_2, NYHA class, LVEF, and VT; patients with a SDNN < 100 ms had higher *1-year mortality* rates than patients with a SDNN > 100 ms
Fauchier et al., 1997[34]	Assess the relationship between HRV and hemodynamic variables and ventricular dysrhythmias for patients with IDC; investigate the prognostic value of HRV	93 patients with IDC; 63 healthy individuals	Patients with IDC had a lower mean RR, SDNN, rmsSD, and day HR:night HR ratio than healthy persons; patients with IDC and class II-IV HF, had a lower mean RR, SDNN, and day HR:night HR ratio than patients with class I HF; mean RR, SDNN, and day HR: night HR ratio correlated with LV shortening fraction, PCWP, and LVEF; in multivariate analysis, decreased SDNN independently predicted *future cardiac events*; SDNN < 100 was associated with *higher mortality* rates
Szabo et al., 1997[65]	Assess the prognostic value of HRV for patients with HF	159 patients with class II-IV HF	In a multivariate model, decreased SDNN and pNN50 predicted *all-cause mortality*; pNN50 < 2% and LFP > 14 ms^2 predicted *death from progressive pump failure*
Jiang et al., 1997[82]	Assess the ability of HRV to predict mortality and life-threatening cardiac events for patients with HF	26 patients with ≥ IIIb HF	Patients who *died* or had a *life-threatening event* had lower SDNN and SDANN values than patients without events; SDNN ≤ 53.4 ms and SDANN ≤ 41.3 ms were associated with shorter *event-free survival*; other clinical measures did not distinguish event-free patients from those who had cardiac events
Nolan et al., 1998[36]	Assess the prognostic value of HRV for patients with HF	433 patients with class I-III HF	SDNN was a univariate and multivariate predictor of *all-cause mortality*; patients with SDNN < 50 msec had highest mortality rates; SDNN was a stronger predictor of *death* related to progressive HF than other conventional clinical parameters
Wijbenga et al.,	Assess the clinical and prognostic value of HRV for patients with HF	64 patients with HF	HRVI was positively associated with LVEF and deceleration time; in a multivariate model that included several clinical parameters,

Author/ Date	Major Purpose of the Study Regarding HRV	Sample	Major Findings Related to Heart Rate Variability for Patients with Heart Failure
1998[83]			HRVI index independently predicted *cardiac death* and *heart transplantation*
Bonaduce et al., 1999[66]	Assess the predictive value of HRV for patients with HF	97 patients with HF	Patients with class III-IV HF had lower time domain (mean RR, SDNN, SDANN index, SDNN index) and frequency domain (ln TP, ln ULFP, ln VLFP, ln LFP, LF:HF ratio) measures of HRV than patients with class II HF; SDNN, SDANN index, pNN50, and LF:HF ratio predicted *mortality* for patients regardless of etiology; the inclusion of HRV data improved the prognostic value of clinical and echocardiographic data
Guzzetti et al., 2000[84]	Determine the prognostic value of spectral and non-linear analysis of HRV	30 patients with HF; 20 healthy individuals	Compared to healthy persons, patients with HF had lower LF (nu) and LF:HF values, higher HFP (nu) values, and a steeper $1/f$ slope; baseline LFP (absolute and nu) was higher and the $1/f$ slope less steep for patients who were *alive* at 15-month follow-up
Galinier et al., 2000[62]	Assess the prognostic value of HRV for all-cause and sudden death	190 patients with class II-IV HF	Non-survivors had lower SDNN, SDANN, SD, ln day-time and ln night-time TP, ln day-time and ln night-time LFP, and ln night-time HFP values; in a multivariate model, SDNN predicted *all-cause death* while day-time ln LFP predicted *sudden death*
Lucreziotti et al., 2000[67]	Assess the interaction between autonomic activity and RV function in severe HF and determine whether this predicts future cardiac events	75 patients with severe HF	The LF:HF ratio was inversely correlated with norepinephrine levels; in a multivariate model that included standard clinical variables, only low LF:HF ratio independently predicted *cardiac death* and *heart transplantation*; TP and LFP were positively correlated with RVEF; HFP was inversely associated with RVEF
Makikallio et al., 2001[1]	Evaluate whether HRV predicts mortality for patients with chronic HF with ventricular dysfunction	499 patients with class II-IV HF and ventricular dysfunction	Mean HR, SDNN, HRVI, VLFP, and short-term fractal exponent (α_1) were univariate predictors of *mortality*; HRV indices were stronger univariate predictors of *mortality* for patients with class II HF than for those with class III or IV HF; after adjusting for other risks such as age and LV function, α_1 predicted *mortality* for patients with class II but not class III or IV HF
Boveda et al., 2001[63]	Assess the prognostic value of time domain measures of HRV for patients with HF	190 patients with class II-IV HF	Survivors had higher SDNN, SDANN, and SD values; in a multivariate model, SDNN independently predicted *all-cause death*

Author/ Date	Major Purpose of the Study Regarding HRV	Sample	Major Findings Related to Heart Rate Variability for Patients with Heart Failure
Bilchick et al., 2002	Evaluate whether HRV could predict SCD in patients with HF	127 patients with class II-IV HF	Patients with SDNN < 65.3 msec had a higher risk of *mortality* and *SCD* than patients with SDNN ≥ 65.3 msec; in a multivariate model containing demographic and clinical variables, only SDNN predicted overall *mortality*
La Rovere et al., 2003	Determine whether HRV predicts SCD for patients with HF	Derivation and validation samples of 202 and 242 patients, respectively, with moderate to severe HF	For the derivation sample, lower LFP during controlled breathing and LVEDD independently predicted *SCD*; in the validation sample, lower LFP during controlled breathing and number of PVCs/hour predicted *SCD*
Aronson et al., 2004	Investigate whether HRV measures predict post-discharge survival for patients admitted with decompensated HF	199 patients with class III-IV HF	In a multivariate model, patients with SDNN, SDANN, TP, and ULFP values < 44 ms, < 37 ms, < 1,475 ms^2, and < 1,100 ms^2 respectively, had higher *mortality* rates; ULFP power was the strongest predictor of *mortality*

Refer to Table 1 for abbreviations; also HRVI = heart rate variability index; LVEDD = left ventricular end-diastolic diameter; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death; SD = mean of the standard deviations of all RR intervals for all 5-minute segments; VT = ventricular tachycardia

Figure Legends

Figure 1: Beat-by-beat heart rate over time from an individual patient. "Cardiotachometer" output shown here resulted from the computer detecting the interval between onset of successive individual heart beats and converting the resultant sequence of RR intervals into visual display of heart rate. Heart rate fluctuated significantly from moment-to-moment. Power spectral analysis is a mathematical process that quantitatively summarizes these fluctuations in terms of frequency and amplitude.

Figure 2: Arterial blood pressure (top, mm HG; recorded non-invasively), RR interval (middle, msec.) and ECG (bottom) show waxing and waning of inter-beat interval over time in this resting subject. This arrhythmia, which originates in sinus node (note P waves preceding each QRS complex) and is in phase with respiration, is known as respiratory sinus arrhythmia. This rhythm appears in the heart rate power spectrum within the "high frequency" region and is mediated by alterations in parasympathetic nervous activity to the SA-node.

Figure 3: Illustrative heart rate power spectrum from an individual patient. Ordinate is power (mm Hg^2) shown here using a linear scale; abscissa is frequency (Hz). High frequency (HF) peak at respiratory rate is widely acknowledged to be under the control of the parasympathetic nervous system, though the precise relationship between changes in cardiac vagal nervous activity and changes in HF power has not been established. Low frequency (LF) peak typically occurs at about 0.1 Hz in the human; the power within the HF region in the heart rate spectrum appears to be jointly controlled by cardiac sympathetic and parasympathetic nervous activity. The very low frequency (VLF) peak has been attributed to slowly varying changes in vasomotor tone, probably related to processes such as thermoregulation.

Figure 1.

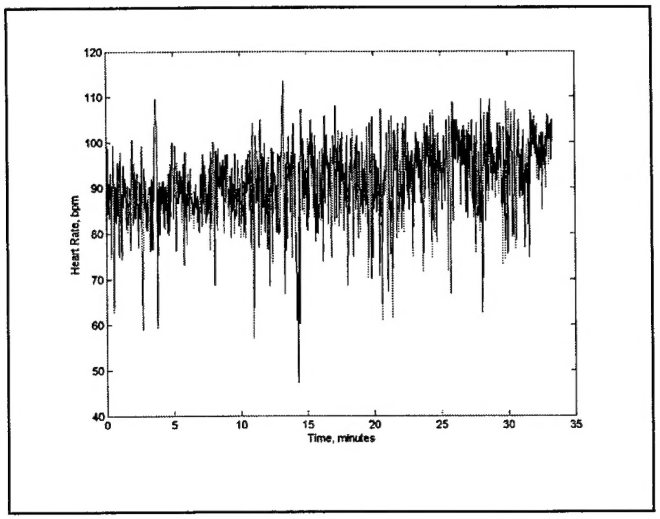

120
110
100
90
80
70
60
50
40
Heart Rate, bpm
0
5
10
15
20
25
30
35
Time, minutes

Figure 2.

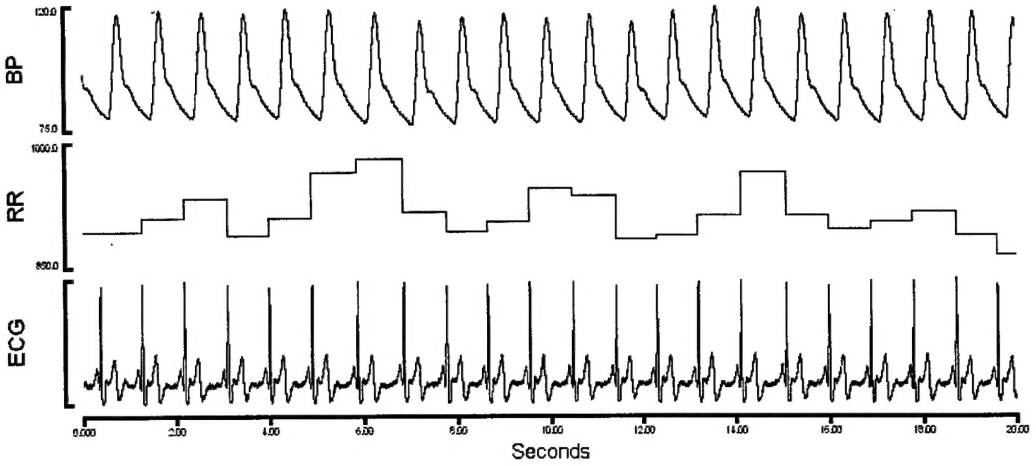
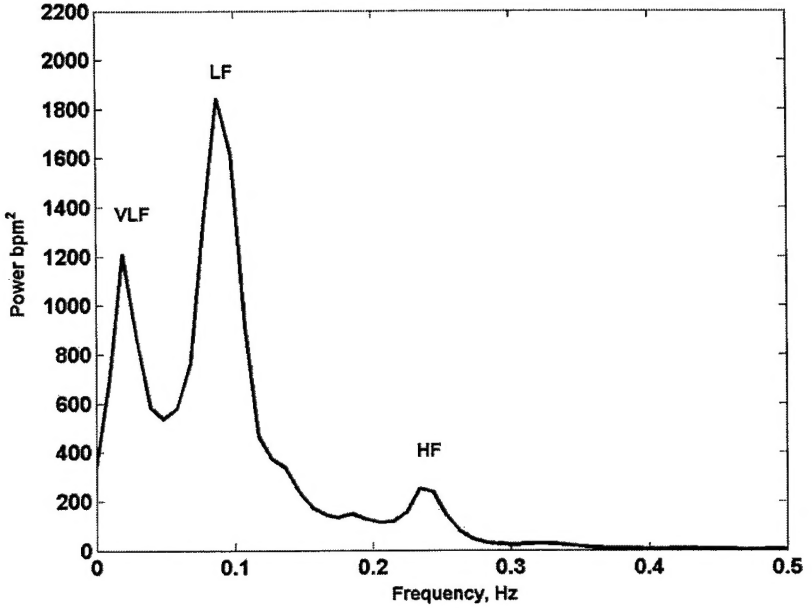


Figure 3.


2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Power bpm²
LF
VLF
HF
0
0.1
0.2
0.3
0.4
0.5
Frequency, Hz